Chapter

Peripartum Cardiomyopathy: The Hidden Enemy

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Abstract

Peripartum cardiomyopathy (PPCM) is the most common cardiomyopathy in pregnancy. It is potentially life-threatening. It is, diagnosed in women without a history of heart disease 1 month before delivery or within 5 months. It is marked by heart failure and left ventricular dyshfunction. The evolution is favorable. LV function improves within 6 months in the majority of patients, but long-lasting mortality and morbidity are not infrequent. Recent work suggests the critical toxic role for late-gestational hormones on the maternal vasculature and the genetic underpinnings of PPCM. Complications include different types of supraventricular and ventricular arrhythmias, heart failure and ischemic stroke. The brain natriuretic peptide (BNP) can be used to risk stratify women for adverse events. Management of peripartum cardiomyopathy is based on treatment of heart failure. The addition of bromocriptine seemed to improve LVEF. Close monitoring of pregnant women with cardiomyopathy by multidisciplinary team is recommended.

Keywords: pregnancy, cardiomyopathy, heart failure

1. Introduction

In the 1800s, heart failure associated with pregnancy and the peripartum period was recognized for the first time by Virchow and others [1]. However, the term peripartum cardiomyopathy (PPCM) was not introduced until 1971 by Demakis and Rahimtoola [2]. Those authors, specifically defined the syndrome as occurring in the peripartum period.

In 2010, the European Society of Cardiology provided operational definition of PPCM as cardiomyopathy with reduced EF, usually <45%, presenting toward the end of pregnancy or in the months after delivery in a woman without previously known structural heart disease [3]. Cardiac imaging before clinical presentation is almost never available in these young women, therefore, the absence of preexisting heart disease is usually only presumed [4].

Why this interest in peripartum cardiomyopathy? It is both the most common cardiomyopathy in pregnancy and the most common non-obstetric cause of maternal death.

The timing of PPCM is not certain. Most cases occur in the first weeks after delivery [2].

However, it can also present well before and up to months after delivery.

These uncertainties make the definition of this disease imprecise and reflects our still incomplete understanding of PPCM.

Many potential causes have been proposed, including autoimmunity, viral myocarditis, nutritional deficiencies, and hemodynamic stresses [5]. Most recently, a role for vascular dysfunction, hormonal insults, and underlying genetics has been suggested. But, the cause of PPCM remains unknown.

Clinical recognition is integral to the management of this disease, because there must be careful exclusion of alternative etiologies. Specific diagnostic or prognostic tests are lacking.

Management of peripartum cardiomyopathy is based on standard heart failure therapy. The addition of bromocriptine seemed to improve LVEF.

2. Epidemiology

The reported incidence of PPCM varies between 1:100 and 1:20 000 deliveries worldwide and between races within countries. Accurate data are lacking because of the paucity of population-based registries.

The Kaiser Permanente Health system, which is the USA's largest non-profit health plan including 9.9 million members, provided data that identified pregnant women with heart failure from 2003 to 2014 [6]. Among these women, PPCM occurred in 333 (68.2%). An analysis of 64 million discharge US hospital records from 1000 hospitals in 47 states identified 34 219 cases of PPCM, with an incidence of 1 in 968 births [7].

A higher incidence of disease is found among African-American woman, who are 3-to 16-fold more likely to be diagnosed with PPCM [8, 9]. The incidence of PPCM in Africa and Asia suggest an incidence of ≈1 in 1000 live births [6]. Women of African descent are more likely to develop PPCM.

However, there are some striking hot spots of PPCM, the cause of which remains unclear. In northern Nigeria, the incidence of PPCM may be as much as 1 in 100 live births [10]. In Haiti, the incidence of PPCM has been reported as high as 1 in 300 live births [11] possibly related to racial background, a high prevalence of preeclampsia or nutritional deficiencies.

An increasing trend of PPCM has been reported in many studies. For example, from 8.5 to 11.8 per 10 000 live births between 2004 and 2011 [7] and from 2.3 to 4.5 per 10 000 live births between 1990 and 2002 [12]. This increasing incidence is probably related to the increased recognition and diagnosis of disease, rising maternal age and multifetal pregnancies, or changing demographics [12, 13].

As the incidence of PPCM increases, the mortality increases as well. In a Californian study of maternal cardiovascular deaths between 2002 and 2006, PPCM was the leading cause (23%) [14].

3. Predisposing factors

Risk factors for PPCM are not understood. Studies have shown that increasing age, African ethnicity, pre-eclampsia, multiparity, malnutrition and traditional risk factors for cardiovascular disease, such as hypertension, diabetes and smoking, are associated with PPCM.

3.1 Age

The incidence of PPCM is associated with age. More than 50% of cases occur in women over 30 years of age [7, 8] with an odds ratio of 10 in a comparison of women less than 20 years of age [7].

Although the disease can strike women of any age, most women in the United States are diagnosed in women older than 30 years [15].

3.2 Race

PPCM affects black women more often. A study in California noted an incidence of PPCM in blacks of 1 in 1421, nearly 3 times that in whites [8].

In a population study of cases in North Carolina in 2003, the incidence of PPCM in black women was 4 times that of white women (1,1087 versus 1,4266), and the fatality rate at 5-year follow-up was also 4 times as high (24% versus 6%) [16].

3.3 Preeclampsia and eclampsia

Preeclampsia strongly predispose to PPCM. However, it is important to realize that PPCM is not simply a manifestation of severe preeclampsia.

A meta-analysis of 22 studies covering 979 cases of PPCM showed an overall prevalence of preeclampsia of 22%, >4 times the 3–5% population prevalence [17]. The prevalence of preeclampsia in many of these studies may be underestimated because preeclampsia is often underreported and because the presence of preeclampsia is often used as an exclusion criterion from the diagnosis of PPCM.

PPCM is also frequently found in association with eclampsia, with an odds ratio of 12.9 in a California population study of 1888 patients with eclampsia [18].

It is important to realize that preeclampsia can also trigger pulmonary edema in the absence of PPCM. The cardiac toxicity caused by preeclampsia can be clinically silent but can also present as pulmonary edema with preserved EF or as part of PPCM. A number of echocardiographic studies have shown that preeclampsia causes diastolic dysfunction even in the absence of clinical heart failure [19]. This diastolic dysfunction is independent from blood pressure elevations and can persist up to 1 year after delivery and resolution of preeclampsia [4].

The strong association between preeclampsia and PPCM suggests that they may share pathophysiological mechanisms. The suspicion for PPCM should never be lowered in the presence of preeclampsia.

3.4 Multiple gestations

Rate of twin births is generally higher in reports of PPCM than in the general population.

PPCM is frequently reported in cases of multigestational status. According to a meta-analysis, the average rate of twin gestations in cases of PPCM across 16 studies was 9% well above the average estimated prevalence of 3% [17, 20].

Although multiparity has traditionally been defined as a risk factor for PPCM, recent studies have shown that the majority of cases of PPCM in the US occur during the first or second pregnancy [2, 15].

3.5 Hypertension

According to a meta-analysis covering 979 cases of PPCM, hypertensive disorder was present in 37% (range, 29–45%) of cases [17]. A study of US hospital discharge records in 6 states identified 535 patients with PPCM, of whom 46.9% had hypertension (odds ratio, 13.4) [21].

We may say that hypertension strongly predispose to PPCM.

3.6 Other factors

Substance abuse, anemia, asthma, diabetes mellitus, obesity, and malnutrition are other associated conditions that have been reported but less well substantiated.

4. Hemodynamic changes during normal pregnancy

4.1 Antepartum changes

During pregnancy, several hemodynamic changes occur [22]:

- *Preload increases:* Maternal blood volume begins to increase at 6 weeks' gestation. By the second trimester, maternal blood volume increases to 50% above baseline. This effect leads to increased preload and left ventricular end-diastolic volume.

- *Afterload decreases:* As the uterine circulation increases during the first trimester, the systemic vascular resistance falls. There is further peripheral vasodilatation that occurs, likely from decreased vascular responsiveness to angiotensin and norepinephrine. These cumulative changes result in a decrease in maternal blood pressure.

- *Heart rate increases*: The heart rate increases by 15–20% by the third trimester (secondary to increased sympathetic tone).

In normal pregnancy, cardiac output increases by 30–50% through increased stroke volume during the first two trimesters. During the second part of pregnancy, cardiac output increases through an increase in heart rate. These changes are illustrated in **Figure 1**.

Cardiac output varies by maternal position. When supine, the gravid uterus can compress the inferior vena cava and impede venous return to heart and the cardiac output can decrease by 25%.

Despite these dramatic hemodynamic alterations, intrinsic left ventricular contractility does not appear to change appreciably [24]. The cardiac atria and ventricles must, however, accommodate the pregnancy-induced hypervolemia.

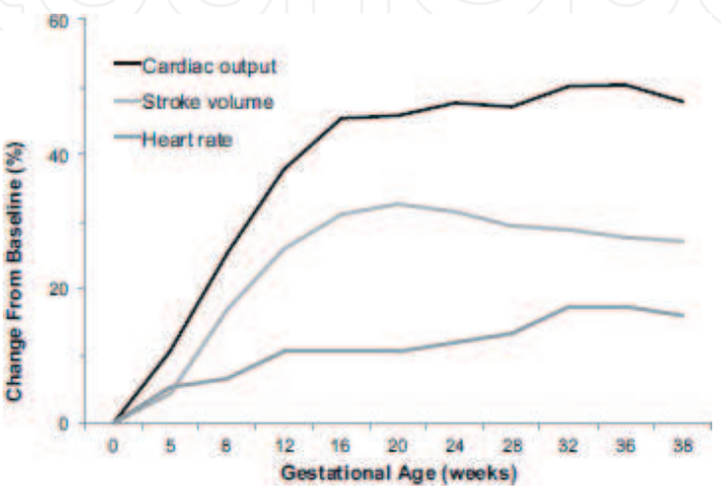

Figure 1.
Changes in hemodynamic properties throughout pregnancy. (data derived from Robson et al. [23]).

Consequently, normal pregnancy is associated with increased left ventricular mass [25, 26]. Such cardiac remodeling is a normal, physiologic response, and some, but not all, suggest these changes resolve by 3 months postpartum [27].

The increase in plasma volume during pregnancy is larger than the increase in red blood cells, which leads to physiological anemia. Systemic vascular resistance decreases at the end of the second trimester and then increases toward the end of pregnancy.

4.2 Labor and delivery

Marked fluctuations in cardiac output occur, during labor and delivery. Each uterine contraction can contribute up to 500 milliliters (ml) of maternal blood volume due to auto- transfusion of uterine blood [22].

Cardiac output can increase as much as 30% during the first stage of labor and up to 50% during the second stage due to maternal pushing [28]. Cardiac output is also augmented by the sympathetic surge induced by anxiety and pain. Immediately after delivery, the cardiac output can increase by 80% above pre-labor values due to auto-transfusion from the uterus during contractions and from the utero-placental circulation after relief of vena caval compression by the uterus. Blood loss during a normal delivery may be 500–1000 mL but is partly compensated by the increase in stroke volume.

Hemodynamic changes are fully reset after 6 months. During pregnancy and postpartum, patients remain in a hypercoagulable state.

5. Physiopathology

Until recently, the etiology and pathophysiology of peripartum cardiomyopathy have been elusive, not fully understood and likely multifactorial.

One of the oldest theories is that PPCM is simply a failed hemodynamic "stress test" of pregnancy. According to this, the cardiovascular changes during pregnancy we detailed before, ultimately lead to peripartum heart failure. We would expect then that PPCM will occur early in midpregnancy, as the maximal changes always start in this period. However, with very few exceptions, PPCM is a disease of late pregnancy and after the delivery. Thus, if peripartum cardiomyopathy were a failed stress test, it would occur much earlier and more often than it does [29].

Another old hypothesis suggested that PPCM is triggered by viral myocarditis. This observation came from findings that right-sided endomyocardial biopsies displayed evidence of inflammation. In a series of endomyocardial biopsies performed in 38 women from Niger (similar proportions of women with PPCM and controls), Inflammation was variably present in endomyocardial biopsies taken from women with the condition, however few patients met histologic criteria for myocarditis [30–32]. Cardiac magnetic resonance (CMR) imaging was performed in a cohort of 40 women in the Investigations in Pregnancy-Associated Cardiomyopathy (IPAC), only one woman had findings potentially consistent with myocarditis [33].

Other potential causes for PPCM have also been proposed. Microchimerism, with fetus-derived cells that can persist in the immune-suppressed pregnant state and can lodge in the maternal heart, has been proposed as a trigger for autoimmunity after delivery [34].

Deficiencies of iron and selenium have also been proposed. The current theory regarding the pathophysiology of peripartum cardiomyopathy suggest that it is genetically predisposed. As previously discussed, this is evidenced epidemiologically by geographic and racial variations. In a German registry, 15% of women

with PPCM had a family history of cardiac disease in a first-degree relative [35]. Genetic studies have supported the notion that genetics contribute to PPCM. Mutations in the TTNC1 and TTN genes that encode cardiac myoprotein troponin C and titin have been identified in women with PPCM [36]. The titin is a critical structural component of sarcomeres in cardiac and skeletal muscle. However, over 90% of individuals with TTN truncating variants do not develop PPCM, indicating that additional environmental, genetic, or epigenetic factors are at play [37].

A landmark 2007 article first introduced that PPCM is a vascular disease triggered by the hormonal changes of late pregnancy. Although the idea was proposed in the past, experimental support for it was lacking. Recently, a 2 mice models and epidemiological data started supporting the notion that PPCM is in large part a vascular disease, triggered by the hormonal milieu of the peripartum [38, 39].

The first mouse lacked the cardioprotective STAT3 gene also accused of developing the peripartum cardiomyopathy. In this case, the oxidative stress led to cleavage of the nursing hormone, prolactin. The 16-kDa prolactin fragment had vasculotoxic and pro- apoptotic properties and vascular and myocardial dysfunction (**Figure 2**) [36].

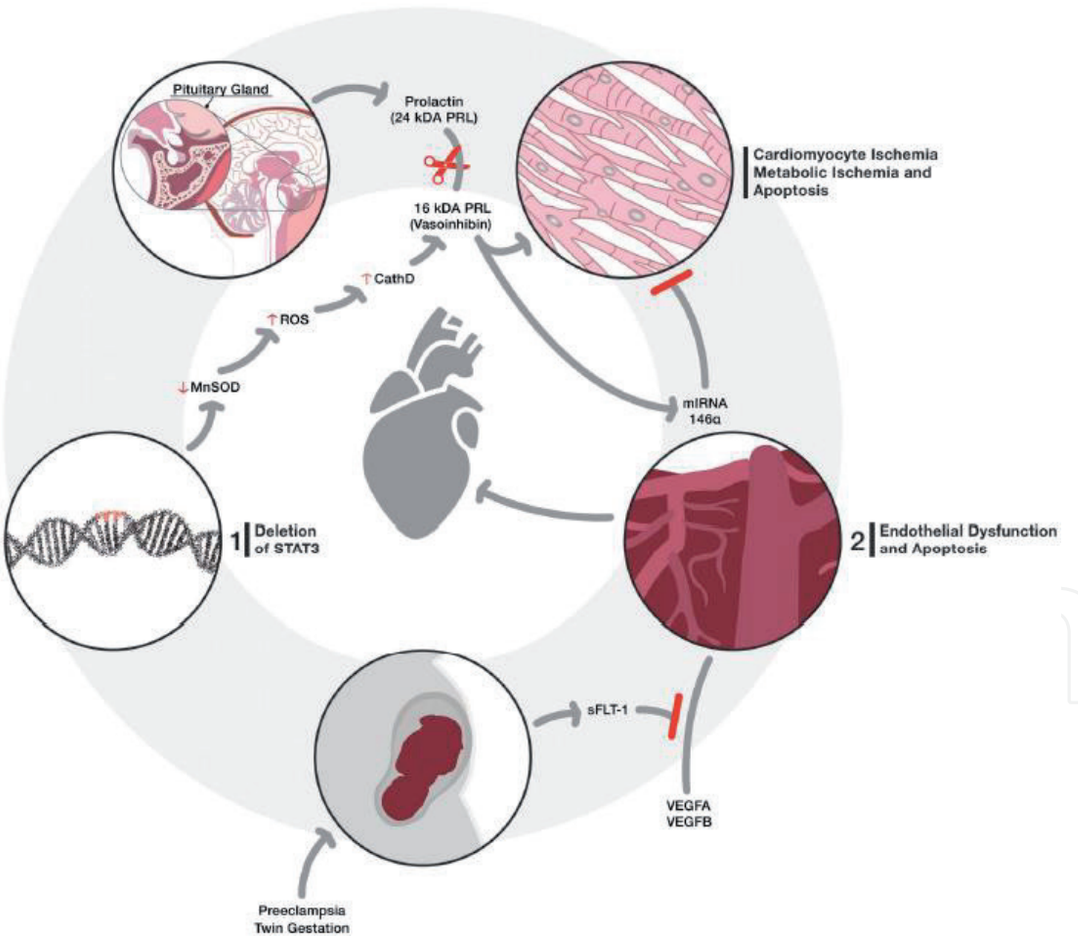

Figure 2.
Pathogenesis of peripartum cardiomyopathy: 1) genetic predisposition caused by mutations of various genes (STAT3, TTN, TTNC1) that regulate cardiomyocyte function causes secretion of cathepsin D (CathD), which cleaves pituitary prolactin (PRL) to form a 16-kDa fragment, vasoinhibin; 2) vasoinhibin acts on blood vessels to trigger apoptosis as well as microRNA-146a resulting in cardiomyocyte ischemia, metabolic insufficiency, and apoptosis. Simultaneously, the placenta, especially with the preeclampsia syndrome, secretes soluble fms-like tyrosine kinase 1 (sFlt-1), which neutralizes vascular endothelial growth factors A and B (VEGFA and VEGFB, respectively) that are critical for vascular health. MnSOD, mitochondrial antioxidant manganese superoxide dismutase; ROS, reactive oxygen species. (data from Arany and Elkayam [4]; Arany [40]. Illustrations created by Ceara Byrne, MS. Commented by Cunningham [29]).

The second mouse had another cardiac-specific genetic deletion of proliferator-activated receptor gamma coactivator-1a (PGC-1a) leading to vasculotoxicity by activation of the 16-kDa prolactin fragment and decreased expression of vascular endothelial growth factor (VEGF) [36]. VEGF is antagonized by the placental secretion of soluble Fms-like tyrosine kinase 1 (sFlt1) which is sufficient to cause profound systolic dysfunction in mice lacking cardiac PGC-1 alpha. This was incriminated in the genesis of PPCM and predicted worse outcomes [41].

6. Clinical presentation

Diagnosis of PPCM may be difficult: the symptoms of heart failure during pregnancy can mimic signs and symptoms that occur during normal pregnancy. The majority of women with PPCM are diagnosed after delivery, precisely in the first month postpartum [3]. Unfortunately, delays in diagnosis are associated with increased incidence of preventable complications and worse outcomes [16, 42, 43].

At the time of diagnosis, patients most commonly complain of signs and symptoms of congestive heart failure including dyspnea, orthopnea and paroxysmal nocturnal dyspnea. Other common symptoms include cough, palpitations, chest tightness, abdominal pain and pitting edema of the lower extremities. If chest pain is severe, the clinical picture can suggest a myocardial infarction or pulmonary embolism.

Women can have difficulty lying flat for the exam. Physical examination usually reveals signs of heart failure including tachypnea, tachycardia, elevated jugular venous pressure, third heart sound, systolic murmur of tricuspid or mitral regurgitation, pulmonary rales, and peripheral edema. Almost half women will have peripartum hypertension and, commonly, Preeclampsia [3, 18, 44]. A minority of patients will present with severe arrhythmias, cardiogenic shock and thromboembolic complications.

7. Diagnostic testing

Initial diagnostic studies will often include an electrocardiogram (ECG), chest x-ray, bloodwork, and echocardiogram. The 12-lead electrocardiogram usually shows only sinus tachycardia with non-specific ST- and T-wave changes. A normal electrocardiogram does not rule out PPCM [45]. A chest x-ray is not obligatory for diagnosis but if it is obtained, fetal shielding must be used. The chest x-ray may show an increased cardiac silhouette with varying degrees of pulmonary congestion, edema and pleural effusions.

Assessment of kidney, liver and thyroid function is recommended along with evaluation for anemia and sepsis. Proteinuria must also be quantified. Levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP, are not change significantly during normal pregnancy [46], they can be mildly elevated in the setting of pre-eclampsia, but they are usually markedly elevated in PPCM [47].

Echocardiography is the gold standard for confirmation of diagnosis and must be obtained as soon as possible. It should be performed in any suspected case of PPCM as the LVEF is typically <45% [3]. It will show global reduction in LV systolic function with various degrees of LV dilatation. In addition to that, it may demonstrate right ventricular dilatation and/or dysfunction, functional mitral and/or tricuspid regurgitation, pulmonary hypertension, and left atrial or biatrial enlargement. Intracardiac thrombus may occur [48, 49], and the LV apex should be

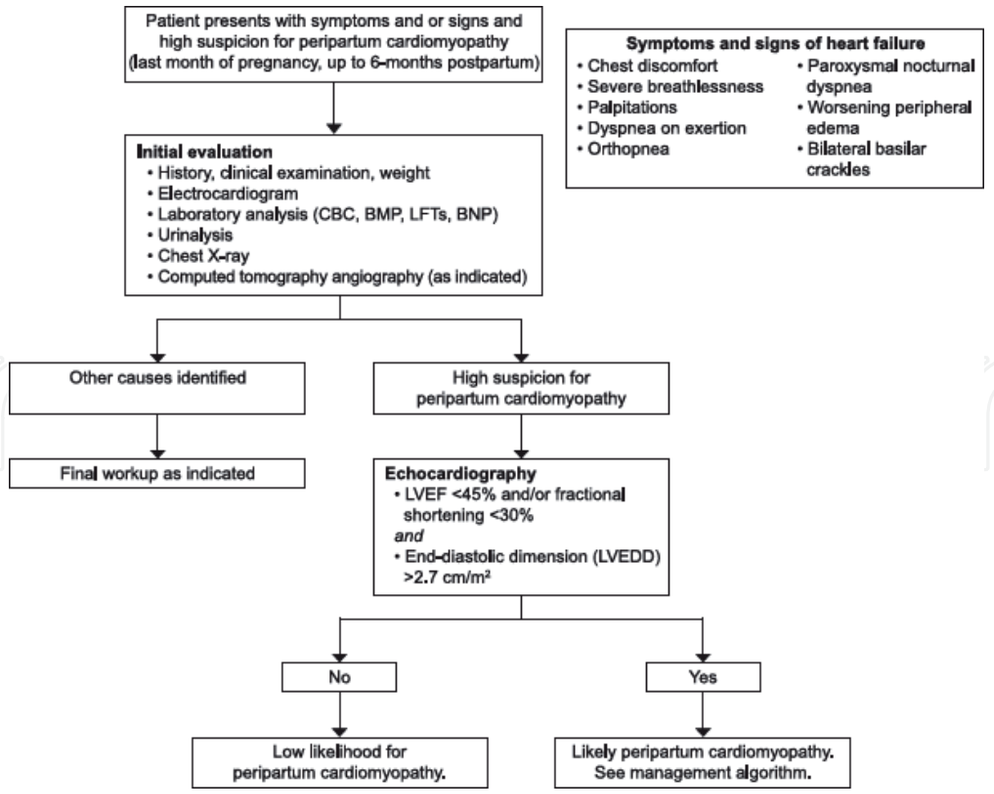

Figure 3.
Evaluation of the woman with suspected peripartum cardiomyopathy. CBC, complete blood count; BMP, basic metabolic panel; LFT, liver function test; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter. (Cunningham [29]).

clearly visualized. In the European worldwide registry of 411 patients, right ventricular function was severely abnormal in 10%, normal in half, mildly abnormal in approximately 35%, and [50]. Hibbard et al. proposed stringent criteria to diagnose peripartum cardiomyopathy [51].

Cardiac magnetic resonance imaging (MRI) provides accurate ejection fraction and chamber measurements when the echocardiogram is inadequate. However, the use of MRI for diagnosis of PPCM is not routine practice as gadolinium should be avoided unless it is considered absolutely essential [52].

There is no role for routine endomyocardial biopsy. The endomyocardial biopsy can only be indicated in the woman for whom there is consideration for heart transplantation.

A summary done by Cunningham of the complete evaluation recommendations are shown in **Figure 3**.

8. Differential diagnosis

PPCM is a diagnosis of exclusion. The differential diagnosis includes common causes of pulmonary edema and cardiac failure. To avoid over diagnosis, careful attention to possible pre-existing heart disease including valvular disease and cardiomyopathies is crucial.

Sepsis syndrome causes endothelial inflammation and can result in myocardial dysfunction from sepsis-induced cardiomyopathy.

Pulmonary causes such as pneumonia facilitated by the immune tolerance during pregnancy or pulmonary embolism resulting from the hypercoagulable peripartum period might mimic a PPCM as well.

Differential Diagnosis	Considerations
Takotsubo cardiomyopathy	Echocardiogram may show classic apical ballooning
Familial cardiomyopathy	Family history, genetic testing
Pre-existing cardiomyopathy	History of HF prior to pregnancy; prior echo studies with low LVEF before pregnancy
Recurrent peripartum cardiomyopathy	Ask about symptoms of HF that occurred after a prior pregnancy
Pre-eclampsia	Preserved systolic function on echocardiogram
Hypertrophic cardiomyopathy	Left ventricular hypertrophy, LVOT obstruction, preserved systolic function, genetic testing
Myocarditis	Consider if viral prodrome, histological diagnosis, fulminant presentation
Arrhythmogenic right ventricular cardiomyopathy	Consider with family history, genetic testing, echocardiographic findings
Left ventricular noncompaction	Echocardiographic and CMR findings
Chemotherapy-related cardiomyopathy	History of chemotherapy, particularly doxorubicin
Valvular heart disease	Echocardiographic findings; congenital aortic stenosis; mitral stenosis from rheumatic heart disease in endemic country. Patients with PPCM may also have valve disease, i.e., mitral regurgitation
Congenital heart disease	May be diagnosed for the first time during pregnancy by echocardiography
Tachycardia-arrhythmia mediated cardiomyopathy	Consider if specific underlying rhythm abnormality. Note that sinus tachycardia may be secondary to heart failure during pregnancy
Hypertensive heart disease	Left ventricular hypertrophy; less common in young people unless very longstanding history of hypertension
Ischemic heart disease	Cardiovascular risk factors; angina; prior CAD; consider SCAD and MINOCA diagnoses
Cardiomyopathy related to other systemic medical diseases	Consider in the appropriate context, i.e., systemic lupus erythematosus, antiphospholipid syndrome, hemochromatosis
Cardiomyopathy related to other acute conditions	May consider if patient has other conditions such as sepsis, treatment in intensive care unit, post-respiratory arrest
Pulmonary embolism	Dyspnea, tachycardia with preserved LVEF

CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; HF, heart failure; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MINOCA, myocardial infarction in non-obstructive coronary arteries; PPCM, peripartum cardiomyopathy; SCAD, spontaneous coronary artery dissection.

Table 1.
Differential diagnosis for heart failure during pregnancy.

Severe preeclampsia can cause pulmonary edema from a capillary– endothelial leak and decreased plasma oncotic pressure, and multifetal gestation and certain tocolytic agents increase this vulnerability. However, PPCM is only diagnosed in the presence of systolic dysfunction.

Other much less common causes of peripartum heart failure include thyrotoxicosis, lupus erythematosus, myocardial infarction and Takotsubo cardiomyopathy. Echocardiography is sufficient to differentiate from these causes.

Potential causes of pregnancy-related HF are listed in **Table 1** [36].

9. Treatment

9.1 Initial management

Patients with PPCM presenting with symptoms of acute severe heart failure require prompt treatment in an intensive care unit. Intravenous diuretics should be given to patients having pulmonary congestion and volume overload. The caution is required if volume control used before delivery to avoid hypotension and impaired uterine perfusion. For rapid diagnosis and decision-making, a pre-specified management algorithm and expert interdisciplinary team are crucial (**Figures 3–5**) [53, 54].

9.2 Chronic heart failure management

In postpartum, Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be used. The Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are contraindicated before delivery, a combination of hydralazine and organic nitrates can be used instead during pregnancy.

During pregnancy, β-Blockade should be considered. to avoid promoting uterine activity, β-1–selective agents can be preferable. Digoxin may be safely used during pregnancy, but its role is currently being debated [55, 56].

9.3 Bromocriptine and cessation of breastfeeding

There's an increase of Serum levels of a fragment of prolactin, called 16 kDa prolactin during the puerperal period. In PPCM patients, the 16 kDa prolactin fragment is overexpressed and is thought to initiate and perpetrate excessive oxidative stress through reactive oxygen species, which then induces apoptosis via ischemia–reperfusion and hypoxia-reoxygenation mechanisms. This increase of 16 kDa prolactin culminates in myocardial dysfunction and symptomatic heart failure [57, 58]. Dopaminergic inhibition of prolactin secretion achieved with bromocriptine, is thought to thwart prolactin's deleterious effects on cardiac function [41].

The addition of bromocriptine to standard heart failure therapy PPCM patients appeared to result in significantly greater improvements in NYHA functional class, LV systolic and diastolic function, degree of functional mitral regurgitation, and low morbidity and mortality in PPCM patients than seen with standard therapy alone [35, 59–62].

Moreover, although bromocriptine stopped lactation in the PPCM patients, the survival and growth of those infants were normal [60].

Bromocriptine can be prescribed in women with symptoms of congestive heart failure, no other identifiable cause for heart failure finded, that developed in the last month of pregnancy or during the first month postpartum, having LVEF failure <35% by transthoracic echocardiography.

According to the guidelines of European Society of Cardiology, the use of Bromocriptine (2.5 mg once daily) for at least 1 week may be considered in uncomplicated cases, while prolonged treatment (2.5 mg twice daily for 2 weeks, then 2.5 mg once daily for 6 weeks) may be considered in patients with EF <25% and/or cardiogenic shock [63].

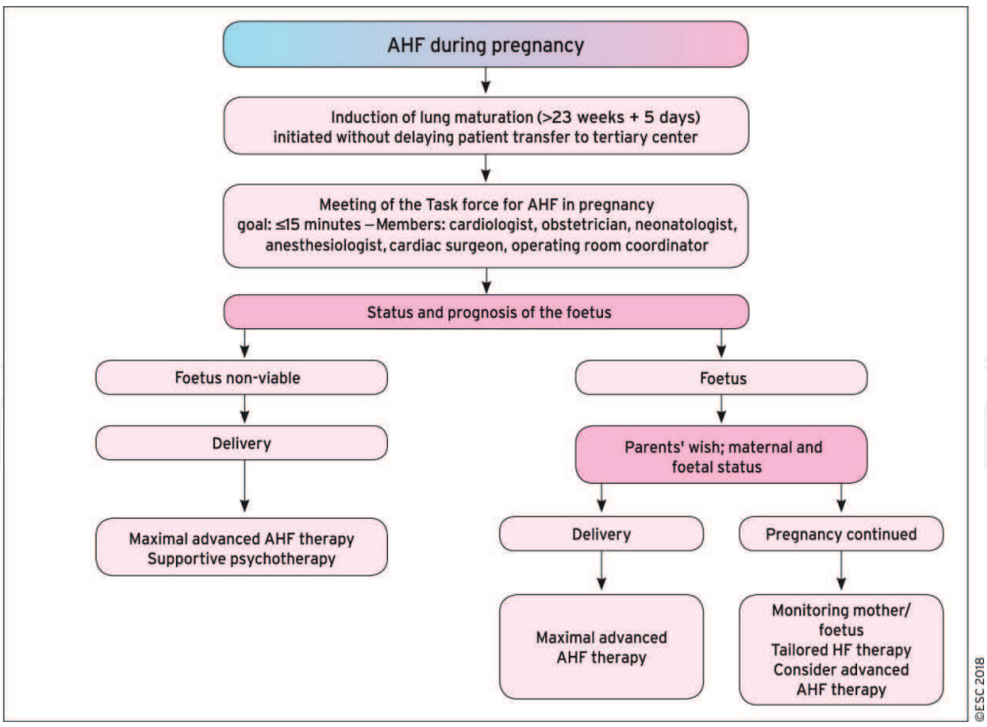

Figure 4.
Management of acute heart failure during pregnancy: Rapid interdisciplinary workup and treatment of mother and foetus (modified from Bauersachs et al. [53]). AHF, acute heart failure; HF, heart failure.

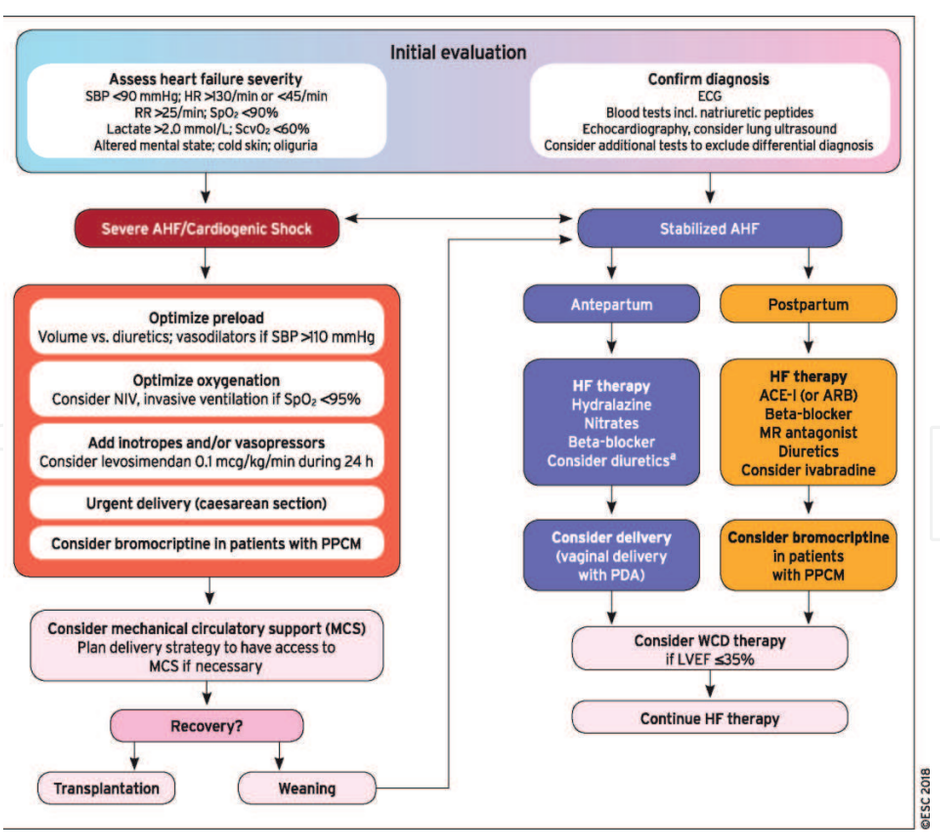

Figure 5.
Management of acute heart failure during/after pregnancy (modified from Bauersachs et al. [53]). A diuretics have to be used with caution due to potential reduction in placental blood flow. ACE-I, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; ECG, electrocardiogram; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MR, mineralocorticoid receptor; NIV, non-invasive ventilation; PDA, Peridural analgesia; PPCM, peripartum cardiomyopathy; RR, respiratory rate; SBP, systolic blood pressure; ScvO2, central venous oxygen saturation; SpO2, peripheral oxygen saturation; WCD, wearable cardioverter-defibrillator.

The bromocriptine should be not prescribed in women with systolic blood pressure > 160 or < 95 mm Hg or diastolic >105 mm Hg; clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers such as sepsis, autoimmune disease, or HIV positivity; significant liver disease (defined as liver transaminase levels>2 times the upper limit of normal); history of peptic ulcer disease; history of psychiatric disorders; impaired renal function (defined as urea and/or creatinine >1.5 times the upper limit of normal [60].

Bromocriptine should not be used in the patient using triptans (for example, for the treatment of migraines), because of theoretical risks of serotoninergic syndrome or prolonged vasospastic reactions.

All patients receiving bromocriptine must receive standard heart failure therapy with at least prophylactic anticoagulation.

9.4 Thromboembolism and anticoagulation

Thromboembolic risk is higher in PPCM than other forms of cardiomyopathy [13]. The peripartum period is a hypercoagulable state [64], likely an evolutionary adaptation to minimize postpartum hemorrhaging. In patients with an LVEF <35%, the anticoagulation must be considered [65], at least during pregnancy and the first 2 months postpartum. Heparin and unfractionated heparin are safe during pregnancy, and the unfractionated heparin is preferred because of its shorter half-life.

9.5 Arrhythmias and antiarrhythmic therapies

Beta-blockers and non-vasoselective calcium-channel blockers can be used safely for rate control of tachyarrhythmias. For PPCM patients, there are no guidelines for implantation of an implantable cardiac defibrillator (ICD). However, sudden cardiac death has been reported in PPCM patients with decreased LVEF in both the acute and chronic stages of this disease, as well as in those whose LVEF has completely normalized, indicating that the risk of sudden cardiac death may persist well into recovery. It might be reasonable to consider ICD in patients with EF <30% with sustained ventricular arrhythmias or history of survival after cardiac arrest, but this decision should be carefully weighed against the evidence that LV function improves within 6 months in the majority of patients. A suitable alternative is wearable cardioverter-defibrillator devices for patients with LVEF ≤35% to prevent sudden cardiac death [66, 67].

But it would be reasonable to consider ICD implantation in patients with persistent NYHA class III or IV symptoms despite optimal medical therapy for 6 months and whose LVEF remains <30%.

9.6 Cardiac assist devices

Temporary circulatory support with inotropes, intra-aortic balloon pumps, LV and biventricular assist devices, and extracorporeal membrane oxygenation must be considered in patients who clinically deteriorate, despite optimal medical treatment, either as a bridge to recovery or transplantation [68]. As that LV function improves within 6 months in the majority of patients, the decision to refer the patient for cardiac transplantation should not be made too early. Results after transplantation in patients with PPCM are comparable to patients transplanted for other etiologies.

9.7 Obstetric management

Excessive volume depletion and angiotensin-converting enzyme inhibitors should be avoided. No published data exist to indicate that elective caesarian

delivery or early delivery can ameliorate PPCM or improve fetal prognosis. Apgar scores, mean birth weight and size, are lower in neonates born to women with PPCM, likely reflecting earlier gestational age at delivery [69]. Timing and mode of delivery must therefore be made by a team of obstetricians and cardiologists. Early delivery needs should be reserved for cases of impending peril to mother or fetus [70].

9.8 Subsequent pregnancies

Several studies highlighted the higher incidence of PPCM in women with high parity [11, 71, 72]. Increased morbidity and mortality is observed during subsequent pregnancies, especially in women with persistent left ventricular dysfunction after the first pregnancy [62–73]. Early contraception should be given in PPCM women [74].

10. Prognosis

The evolution is favorable. LV function improves within 6 months in the majority of patients and will remain stable under drug treatment. The decision to refer the patient for cardiac transplantation estimated at 1–2% [12]. Prognosis of PPCM is better than the prognosis of other forms of dilated cardiomyopathy [75].

Mortality to 12 months is 4–14% [76, 77]. the addition of bromocriptine to standard heart failure therapy appeared to improve LVEF. A trial adding the prolactin blocker bromocriptine with standard therapy for heart failure reported an excellent 6-month follow-up outcome in severely diseased patients having over 60% full recovery and 0%, heart transplantation, use of assist device and mortality [60].

Mortality between 2 and 5 years, ranging from 0 to 6% in American and French women [48–79], to 15–30% in women from Brazil, [80], China, [81] South Africa, [82] Turkey, [83–85] and the Philippines [86].

In USA the mortality ranging from 7 to 16% at between 7 and 8.6 years [16, 75, 77], the mortality was 23% at 6.1 years in India [87]. In Malaysia the mortality was 8.3% at 6.4 years [88].

When myocardial recovery occurs in PPCM, There are no recommendations to determine the time of long-term treatment.

11. Conclusion

Management of peripartum cardiomyopathy is largely limited to the same neurohormonal antagonists used in other forms of cardiomyopathy, the addition of bromocriptine to standard heart failure therapy seemed to improve LVEF. LV function improves within 6 months in the majority of patients having optimal medical therapy. Whatever the evolution, long-term follow-up is essential. Early contraception should be given in PPCM women.

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